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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: September 9, 2009

SUBJECT: **Thiamethoxam: Occupational and Residential Exposure Assessment** for Amendment to Flagship® 25 WG Registered Label for use of Thiamethoxam on Cucurbits, Fruiting Vegetables Grown for Transplant, Ornamentals, Non bearing Fruit and Nut Trees and Christmas Trees

PC Code: 060109
Decision No.: 407002
Petition No.: NA
Risk Assessment Type: Single Chemical
TXR No.: NA
MRID No.: 46402915, 46033991

DP Barcode: D365499 and D364271
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I. EXECUTIVE SUMMARY

Thiamethoxam is a systemic insecticide belonging to the neonicotinoid class of chemistry. It is used to treat various agricultural crops, turf grass, sod farms, golf course, residential lawns, indoor crack and crevice use, ornamental plants grown in greenhouses, and Christmas trees. The registrant, Syngenta, has requested an amendment to the Flagship® 0.25 WG label to 1) increase the maximum annual application rate to 0.266 lb ai/acre/year from 0.0125 lb ai/acre/year for use on ornamental plants, fruit and nut trees, Christmas trees, forest seedlings and 2) add the use on fruiting and cucurbit vegetables plants grown for transplant and for re-sale to consumers. Thiamethoxam may be applied as a foliar application and/or to soils and soil-less mediums using ground or aerial equipment, chemigation, backpacks, foggers and other hand-held sprayers. Based on application rates and label information, exposure is expected to occur for short- and intermediate-term durations.

Hazard Characterization

Thiamethoxam is classified as Toxicity Category III for acute oral toxicity and Category IV for acute dermal, inhalation toxicity and eye irritation. Thiamethoxam is not a dermal sensitizer.

The oral NOAEL of 8.23 mg/kg/day (point of departure for all durations) is based on slightly prolonged prothrombin times and decreased plasma albumin and A/G ratio (both sexes); decreased calcium levels and ovary weights and delayed maturation in the ovaries; decreased cholesterol and phospholipid levels, testis weights, spermatogenesis, and spermatic giant cells in testes from a 90-day oral study in the dog. The LOAEL ranged from 32 mg/kg/day in males to 33.9 mg/kg/day in females.

The adult dermal NOAEL of 1.2 mg/kg/day (point of departure for all durations) is based on sperm abnormalities and testicular effects observed after *in utero* and post-natal exposure in the rat reproduction studies. Although a 21-day dermal toxicity study in rats is available, HED selected a reproductive NOAEL because the reproductive parameters are not evaluated in the dermal toxicity study and thus the consequences of these effects cannot be ascertained for the dermal route of exposure.

The infants and children's (1-6 years) dermal NOAEL of 60 mg/kg/day (point of departure for all durations) is based on increased plasma glucose, triglyceride levels, and alkaline phosphatase activity and inflammatory cell infiltration in the liver and necrosis of single hepatocytes in females from a 28-day dermal toxicity study in rats. The LOAEL is 250 mg/kg/day (females).

The inhalation NOAEL of 1.2 mg/kg/day (point of departure for all durations) is based on sperm abnormalities and testicular effects observed after *in utero* and post-natal exposure in the rat reproduction studies. Since no data are available to indicate how much exposure will induce the effects, the effects are considered to be appropriate for all exposure durations. Other than acute toxicity, no inhalation studies are available. Therefore, the reproductive endpoint is selected for inhalation exposure.

For all exposure scenarios, uncertainty factors (UF) of 10x for interspecies and 10x for intraspecies variation (total UF of 100x) were used. Therefore, for all occupational and residential exposure scenarios, the level of concern for the margin of exposure (MOE) is 100.

Cancer Assessments:
Thiamethoxam is classified as **"Not Likely to be Carcinogenic to Humans"** based on convincing evidence that a non-genotoxic mode of action for liver tumors was established in the mouse and that the carcinogenic effects are a result of a mode of action dependent on sufficient amounts of a hepatotoxic metabolite produced persistently. Quantification of cancer risk is not required.

FQPA and Uncertainty Factors
Based upon the hazard data and the methods used to estimate exposure, it is recommended that the 10X FQPA SF for the protection of infants and children be reduced to 1X.

Residential Exposure:
An indoor crack and crevice product, Optigard™ Insecticide, is registered for thiamethoxam since the 2007 Residential Exposure Assessment. The registered label indicates that thiamethoxam is applied by commercial applicators only. Therefore, a quantitative assessment for handler exposure was performed for commercial applicators only and is addressed in the occupational exposure section. However, a residential postapplication exposure assessment for adults and toddlers was conducted. Since thiamethoxam has a very low vapor pressure, 4.95 x 10^{-11} mm Hg, inhalation exposure is expected to be negligible as a result of indoor crack and crevice use. Therefore, a quantitative postapplication inhalation exposure assessment was not performed. All postapplication dermal and incidental oral indoor crack and crevice scenarios resulted in MOEs greater than 100 and are not of concern to HED.

Combined Residential Exposure and Risk
A revised combined residential assessment based on indoor crack and crevice use has been provided for this assessment. HED combined all non-dietary sources of postapplication exposure to obtain an estimate of potential combined residential exposure. All combined postapplication scenarios resulted in MOEs greater than 100 and were not of concern to HED.

Occupational Exposure:
Occupational exposure and risk resulting in MOEs greater than or equal to 100 are not of concern to HED. All occupational handler scenarios resulted in total MOEs greater than the level of concern (MOEs $\geq$ 100). With the exception of the flagger scenario, the calculated MOEs include use of personal protective equipment (PPE) (gloves; also respirator and eye ware for the fogger use) or engineering controls for aerial applicators. All postapplication scenarios resulted in MOEs greater than or equal to 100 and therefore are not of concern to HED.

Restricted Entry Interval
The restricted entry interval (REI) is based on the acute toxicity of thiamethoxam technical material which is classified as Category III for acute oral and Category IV for acute dermal and eye irritation. Thiamethoxam is not a dermal sensitizer. Acute toxicity categories III and IV

chemicals require a 12- hour REI. Therefore, the 12-hour REI which appears on the proposed label is adequate.

Review of Human Research
This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, which comprise the Pesticide Handlers Exposure Database (PHED) have been determined to require a review of their ethical conduct, and have received that review.

2.0. HAZARD CHARACTERIZATION

2.1 Hazard Profile

The database for acute toxicity for thiamethoxam is complete and is summarized below in **Table 2.1a.** Thiamethoxam is classified as Toxicity Category III for acute oral toxicity and Category IV for acute dermal, inhalation toxicity and eye irritation. Thiamethoxam is not a dermal sensitizer.

The oral NOAEL of 8.23 mg/kg/day (point of departure for all durations) is based on slightly prolonged prothrombin times and decreased plasma albumin and A/G ratio (both sexes); decreased calcium levels and ovary weights and delayed maturation in the ovaries; decreased cholesterol and phospholipid levels, testis weights, spermatogenesis, and spermatic giant cells in testes from a 90-day oral study in the dog. The LOAEL ranged from 32 mg/kg/day in males to 33.9 in females.

The adult dermal NOAEL of 1.2 mg/kg/day (point of departure for all durations) is based on sperm abnormalities and testicular effects observed after *in utero* and post-natal exposure in the rat reproduction studies. Although a 21-day dermal toxicity study in rats is available, HED selected a reproductive NOAEL because the reproductive parameters are not evaluated in the dermal toxicity study and thus the consequences of these effects cannot be ascertained for the dermal route of exposure.

The infants and children's (1-6 years) dermal NOAEL of 60 mg/kg/day (point of departure for all durations) is based on increased plasma glucose, triglyceride levels, and alkaline phosphatase activity and inflammatory cell infiltration in the liver and necrosis of single hepatocytes in females from a 28-day dermal toxicity study in rats. The LOAEL is 250 mg/kg/day (females).

The inhalation NOAEL of 1.2 mg/kg/day (endpoint for all durations) is based on sperm abnormalities and testicular effects observed after *in utero* and post-natal exposure in the rat reproduction studies. Since no data are available to indicate how much exposure will induce the effects, the effects are considered to be appropriate for all exposure durations. Other than acute toxicity, no inhalation studies are available. Therefore, the reproductive endpoint is selected for inhalation exposure.

On April 27, 2005 the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met to re-evaluate the carcinogenic potential of thiamethoxam. In accordance with the EPA's Final Guidelines for Carcinogen Risk Assessment (March, 2005), the CARC classified Thiamethoxam as **"Not Likely to be Carcinogenic to Humans"** based on convincing evidence that a non-genotoxic mode of action for liver tumors was established in the mouse and that the carcinogenic effects are a result of a mode of action dependent on sufficient amounts of a hepatotoxic metabolite produced persistently. Quantification of cancer risk is not required.

A summary of the toxicological doses and endpoints is provided in **Table 2.1b**.

2.2 FQPA and Uncertainty Factor Considerations

Based upon the hazard data and the methods used to estimate exposure, it is recommended that the 10X FQPA SF for the protection of infants and children be reduced to 1X. There is no quantitative or qualitative evidence of increased susceptibility of rat or rabbit fetuses to *in utero* exposure to thiamethoxam in the developmental toxicity studies. The developmental NOAELs are either higher than or equal to the maternal NOAELs. The Developmental Neurotoxicity (DNT) workgroup concluded there was no evidence of increased susceptibility in the DNT study in rats, based on evaluation of additional brain morphometric data for the low- and mid-dose pups (January 17, 2007 meeting). Although there is evidence of increased quantitative susceptibility for male pups of both two generation reproductive studies, NOAELs and LOAELs were established in these studies, and the Agency selected the NOAEL for testicular effects in F1 pups as the basis for risk assessment. The Agency has confidence that the NOAEL selected for risk assessment is protective of the most sensitive effect (testicular effects) for the most sensitive subgroup (pups) observed in the toxicological database.

Table 2.1a Acute Toxicity Profile of Thiamethoxam

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral [rat]	44703314	LD_{50}: 1563 mg/kg	III
870.1200	Acute dermal [rabbit]	44703316	LD_{50} = 13.3 g/kg	IV
870.1300	Acute inhalation [rat]	44703317	LC_{50} > 3.72 mg/L	IV
870.2400	Acute eye irritation [rabbit]	44703318	PIS = 10 at 1 hr PIS = 0 at 24 hr Minimally irritating	IV
870.2500	Acute dermal irritation	44703319	PIS = 0	IV
870.2600	Skin sensitization	44710401	Is not a sensitizer using method of Magnusson and Kligman	N/A

Table 2.1b Toxicological Doses and Endpoints for Thiomethoxam for Use in Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Incidental Oral (all durations)	NOAEL= 8.23 mg/kg/day	UF_A= 10x UF_H= 10x SF_{FQPA}=1	MOE= 100 (residential and occupational)	**90-day Dog Study** LOAEL= 32 (males) 33.9 (females) mg/kg/day based on slightly prolonged prothrombin times and decreased plasma albumin and A/G ratio (both sexes); decreased calcium levels and ovary weights and delayed maturation in the ovaries (females); decreased cholesterol and phospholipid levels, testis weights, spermatogenesis, and spermatic giant cells in testes (males).
Dermal (all durations) (Adults)	Oral study NOAEL= 1.2 mg/kg/day (dermal absorption rate = 5%)	UF_A= 10x UF_H= 10x SF_{FQPA}=1	MOE= 100 (residential and occupational)	**2-Generation reproduction study (MRID 44718707)** LOAEL = 1.8 mg/kg/day based on increased incidence and severity of tubular atrophy in testes of F1 generation males. **2-Generation reproduction study (46402904)** LOAEL = 3 (males), not determined (females) mg/kg/day based on sperm abnormalities in F1 males.
Dermal (all durations) (infants/ children 1-6 yrs)	Dermal Study NOAEL=60 mg/kg/day	UF_A= 10x UF_H= 10x SF_{FQPA}=1	MOE= 100 (residential and occupational)	**Rat 28-Day Dermal Toxicity Study** LOAEL = 250 (females) mg/kg/day based on increased plasma glucose, triglyceride levels, and alkaline phosphatase activity and inflammatory cell infiltration in the liver and necrosis of single hepatocytes in females.
Inhalation (all durations)	Oral study NOAEL= 1.2 mg/kg/day (inhalation absorption rate = 100% of oral absorption)	UF_A= 10x UF_H= 10x SF_{FQPA}=1	MOE= 100 (residential and occupational)	**2-Generation reproduction study(MRID 44718707)** LOAEL = 1.8 mg/kg/day based on increased incidence and severity of tubular atrophy in testes of F1 generation males. **2-Generation reproduction study (46402904)** LOAEL = 3 (males), not determined (females) mg/kg/day based on sperm abnormalities in F1 males.

Cancer (oral, dermal, inhalation)	**"Not Likely to be Carcinogenic to Humans"** based on convincing evidence that a non-genotoxic mode of action for liver tumors was established in the mouse and that the carcinogenic effects are a result of a mode of action dependent on sufficient amounts of a hepatotoxic metabolite produced persistently. Quantification of cancer risk is not required.

3.0 AMENDMENTS TO REGISTERED AND PROPOSED USE PATTERNS

Table 3 provides a summary of the proposed amended uses for Flagship® 25 WDG.

Table 3: Proposed Use Pattern for Thiamethoxam

Use Sites		Method of Application	Maximum Application Rate	Timing of Application
Flagship® (25% ai.); Water dispersible granule				
Ornamental plants	Grown in greenhouses, lath and shadehouses, containers, field nurseries and interiorscapes	Aerial, groundboom, chemigation, backpack, low pressure handwand, high pressure handwand, fogger	0.266 lb ai/A or 0.00133 lb ai/gal	For foliar and soil applications, reapply as needed, but no sooner than every 7 days. For applications to soil or other growing media, apply as broadcast, band or drench.
Forest seedlings				
Christmas trees		Aerial, airblast, chemigation, backpack, low pressure handwand, high pressure handwand, fogger		
Non-bearing fruit and nut trees		Airblast, chemigation, backpack, low pressure handwand, high pressure handwand, fogger		
Grass and turf around container grown plants and areas surrounding nurseries and greenhouses		Groundboom, handgun	0.266 lb ai/A or 0.03 lb ai/5000 ft2	
Fruiting vegetable/ cucurbit plant seedlings		Groundboom, chemigation, backpack, low pressure handwand, high pressure handwand	0.086 lb ai/A or 0.0098 lb ai/5000 ft2	
Fire Ant Mounds		Watering can	0.0047 lb ai/gal	

4.0 RESIDENTIAL (NON-OCCUPATIONAL) EXPOSURE/RISK PATHWAY

Residential exposure assessments were previously performed for the use thiamethoxam on turf (M. Collantes; March 2007; D332064) and indoor crack and crevice applications (M. Collantes, July 2009, D359462). The product labels indicate that thiamethoxam is applied by commercial applicators only. Therefore, a quantitative assessment for handler exposure was performed for commercial applicators only. However, residential postapplication exposure assessments for adults and toddlers were conducted.

Since thiamethoxam has a very low vapor pressure, 4.95×10^{-11} mm Hg, inhalation exposure is expected to be negligible; therefore, a quantitative postapplication inhalation exposure assessment was not performed. All postapplication dermal and oral scenarios associated with turf and indoor crack and crevice uses resulted in MOEs greater than 100 and are not of concern to HED.

4.1 Combined Residential Exposure and Risk

A revised combined residential assessment based on indoor crack and crevice use was performed in the July 2009 thiamethoxam residential assessment (M. Collantes, July 2009, D359462). HED combined all non-dietary sources of postapplication exposure to obtain an estimate of potential combined residential exposure. All combined postapplication scenarios resulted in MOEs greater than 100 and were not of concern to HED. A summary of the combined residential exposure assessment is provided in Table 4.1.

Table 4.1. Combined Residential Exposure and Risk Estimates from the Indoor Crack and Crevice Use

Postapplication Scenarios	Daily Dose (mg/kg/day) [1]	MOE [2]	Combined MOE [3]
Short-term			
Adult Dermal – indoor surface	0.0027	430	430
Toddler Dermal - indoor surface	0.08	750	610
Hand-to-Mouth	0.00267	3100	
Intermediate-term			
Adult Dermal - indoor surface	0.027	430	430
Toddler Dermal - indoor surface	0.08	750	680
Hand-to-Mouth	0.001267	6500	

[1] Daily Dose = see Tables 4.2.2.2 and 4.2.2.3

[2]. Adult Dermal MOE = $\frac{\text{NOAEL (1.2 mg/kg/day)}}{\text{Dermal Dose}}$ Child Dermal MOE = $\frac{\text{NOAEL (60 mg/kg/day)}}{\text{Dermal Dose}}$

Hand-to-Mouth MOE = $\frac{\text{NOAEL (8.23 mg/kg/day)}}{\text{Oral Dose}}$

[3] Toddler Combined MOE = $1/ [(1/MOE_{Dermal}) + (1/MOE_{Hand\text{-}to\text{-}Mouth})]$

4.2 Other (Spray Drift)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for thiamethoxam.

The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

5.0. OCCUPATIONAL EXPOSURE

This occupational assessment will provide exposure risk estimates for both handler and postapplication exposure scenarios for the product, Flagship®, containing 25% of the active ingredient thiamethoxam and formulated as a water dispersible granule.

5.1 Handler (Agricultural and Commercial) Exposure

Thiamethoxam may be applied to the soil and/or foliage by ground or aerial equipment, chemigation, backpack, low pressure handwand, fogger and/or other various handheld equipment. Application methods, rates, intervals, and use sites are summarized in Table 3. Handler exposure is expected to be short- and intermediate-term based on information provided on proposed labels. The quantitative exposure/risk assessment developed for agricultural and commercial handlers is based on the following exposure scenarios:

Mixer/Loaders

- Mixing/loading dry flowable for groundboom for use on fruiting vegetables, cucurbits, ornamentals, non-bearing fruit and nut trees, Christmas trees and seedling grown in nurseries and grass surrounding nursery pots
- Mixing/loading dry flowable for airblast for use on non-bearing fruit and nut trees grown in nurseries
- Mixing/loading dry flowable for chemigation for use on fruiting vegetables, cucurbits, ornamentals, non-bearing fruit, nut and Christmas trees and seedling grown in nurseries
- Mixing/loading dry flowable for aerial for use on fruiting vegetables, cucurbits, ornamentals, non-bearing fruit, nut and Christmas trees and seedling grown in nurseries

Applicators

- Applying liquid by groundboom to the above mentioned sites, grass and turf surrounding potted plants and nursery
- Applying liquid by airblast to non-bearing fruit and nut trees grown in nurseries
- Applying liquid by aerial application to the above mentioned sites
- Applying liquid by backpack to fruiting vegetables, cucurbits, ornamentals, non-bearing fruit and nut trees, Christmas trees and seedling grown in nurseries, turf and grass

- Applying liquid by handwand or handgun to fruiting vegetables, cucurbits, ornamentals, non-bearing fruit and nut trees, Christmas trees and seedling grown in nurseries, turf and grass

Mixer/loader/applicator

- Mixing/loading/applying dry flowable for backpack on fruiting vegetables, cucurbits, ornamentals, non-bearing fruit and nut trees, Christmas trees and seedling grown in nurseries
- Mixing/loading/applying dry flowable for low pressure handwand on fruiting vegetables, cucurbits, ornamentals, non-bearing fruit and nut trees, Christmas trees and seedling grown in nurseries
- Mixing/loading/applying dry flowable for high pressure handwand on fruiting vegetables, cucurbits, ornamentals, non-bearing fruit and nut trees, Christmas trees and seedling grown in nurseries
- Mixing/loading/applying dry flowable for hose-end sprayer on grass surrounding potted plants in and around nursery

Flagger

Data and Assumptions for Handler Exposure Scenarios

Unit Exposures:

- Chemical-specific data for assessing exposure during pesticide handling activities (typical mixing/loading and applying) were not submitted to the Agency in support of this Section 3 application. It is HED policy to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 to assess handler exposures for regulatory actions when chemical-specific data are not available (HED Science Advisory Council for Exposure, SOP Number .007, January 1999).

- In greenhouses (GHs), most spray applications are made during late afternoon and into the night, when other workers are not present in the greenhouses. The large scale GH grower set up is often two-20 acre greenhouses. There are greater than 1000 pathways in a typical 40-acre greenhouse. In order to apply a foliar application to 40 acres, workers would have to travel a total of 121 miles up and down all of the pathways. This requires 40 hours, which is equivalent to 5 nights at 8 hours each. In contrast, aerial application to the same area would only take approximately 20 minutes. Therefore, foliar applications within greenhouses are often the least desirable application technique. Large growers all use motorized carts fitted with spray booms, which travel on the double railed heat pipes between each row of plants. Fully automatic carts are common, where the operator only has to monitor these carts from the center roadway and move them from row to row. Nozzles can be opened or closed to direct the spray at the target plant area. Electrostatic sprayers are used in some locations. Volumes of spray applied depend upon the target disease and leaf area, but are typically between 100 - 200 gallons per acre. Foliage treatment within greenhouses may also be performed using ultra low volume (ULV) equipment and thermal foggers. ULV sprayers atomize the spray mixture, which is distributed through the greenhouse using air circulation fans. Remote operation is

possible if the greenhouse configuration permits. Air circulation is required to use this effectively in greenhouses. Thermal foggers use heat to vaporize the spray mixture, creating a fog that remains suspended for a longer time than ULV applications. By moving the fogger along the center roadway, in most greenhouses the fog can penetrate throughout the greenhouse without the need for additional fans (pselina@villagefarms.com). HED does not have specific unit exposures values for these scenarios; however, HED has used surrogate exposure values for groundboom, airblast and handheld sprayer equipment to estimate exposure resulting from these types of indoor greenhouse equipment.

- The proposed registered label indicates foggers as a method of application in greenhouse. Currently HED does not have unit exposure values for this type of application in greenhouse. HED used unit exposure values from the PHED high pressure handwand scenario in addition to a protection factor (PF) 10 respirator and protective eye ware to simulate exposure. We assume a 90% protection factor is provided by a NIOSH-approved half-face cartridge or canister respirator or a powered air-purifying respirator (PAPR).

- There are three basic risk mitigation approaches considered appropriate for controlling occupational exposure. These include administrative controls, use of personal protective equipment (PPE), and the use of engineering controls. Occupational handler exposure assessments were completed by HED using baseline, PPE and engineering controls.

- The baseline clothing level for occupational exposure scenarios is generally an individual wearing long pants, a long-sleeved shirt, shoes, socks, no chemical-resistant gloves, and no respirator. The first level of mitigation generally applied is PPE which includes addition of chemical resistant-gloves, additional layer of clothing and a respirator. The next layer of mitigation considered in the risk assessment process is the use of appropriate engineering controls, which, by design, attempt to eliminate the possibility of human exposure. Examples of commonly used engineering controls include closed tractor cabs, closed mixing/loading transfer systems, and water-soluble packets.

Area Treated – based on HED Exposure Science Advisory Committee SOP Number 9.1

- 80 acres of various agricultural crops were treated with groundboom
- 350 acres of various agricultural crops and sites treated by aerial equipment
- 350 acres of various crops and sites treated by chemigation
- 40 acres of non-bearing fruit and nut trees treated with airblast
- 350 acres for flaggers
- 40 gallons a day was used to treat various crops and sites with backpack or other hand held equipment
- 1000 gallons a day for high pressure handwand

Application Rate:

- The maximum application rate for each proposed product is summarized in Table 3.

Body Weight:

- The average adult female weight of 60 kg was used for estimating dermal and inhalation exposure since the endpoint was based on testicular effects in male pups (F1 generation) seen in two different 2-generation reproductive studies.

Dermal Absorption Factor:

- Since the adult dermal endpoint was based on an oral study, a 5% dermal absorption factor was used to estimate dermal exposure for all durations.

Equations and Calculations:

- **Daily Dose:** Daily dose (inhalation or dermal) was calculated by normalizing the daily dermal or inhalation exposure value by body weight and accounting for dermal or inhalation absorption. For adult handlers using thiamethoxam, the average adult female body weight of 60 kilograms was used for exposure scenarios. Since the dermal toxicological endpoint of concern is based on an oral study, a 5% dermal absorption factor is needed for dermal dose calculations. Since the inhalation toxicological endpoint of concern is based on an oral study, 100% absorption factor is needed for inhalation dose calculations. Daily dose was calculated using the following formula:

$$\textit{Average Daily Dose (mg/kg/day)} = \textit{Daily Exposure (mg ai/day)} \times \frac{\{\textit{Absorption Factor (\%/100)}\}}{\textit{Body Weight (kg)}}$$

Where:

Average Daily Dose	=	Absorbed dose received from exposure to a pesticide in a given scenario (mg pesticide active ingredient/kg body weight/day)
Daily Exposure	=	Amount (mg ai/day) deposited on the surface of the skin that is available for dermal absorption or amount inhaled that is available for inhalation absorption;
Absorption Factor	=	A measure of the amount of chemical that crosses a biological boundary such as the skin or lungs
Body Weight	=	Body weight determined to represent the population of interest in a risk assessment.

Margin of Exposure: the calculations of daily dermal dose and daily inhalation dose received by handlers were then compared to the appropriate endpoint (i.e., NOAEL) to assess the total risk to handlers for each exposure route within the scenarios. All MOE values were calculated separately for dermal and inhalation exposure levels using the following formula:

$$\textit{MOE} = \frac{\textit{NOAEL (mg/kg/day)}}{\textit{Average Daily Dose (mg/kg/day)}}$$

Where:

MOE	=	Margin of exposure value used by HED to represent risk or how close a chemical exposure is to being a concern (unitless)

ADD = Average daily dose is absorbed dose received from exposure to pesticide
NOAEL = Dose level in a toxicity study, where no observed adverse effects occurred in the study

Total MOE: When the dermal and inhalation endpoints, effects and routes of exposure are the same the doses may be added together to determine a total dose and MOE using the following formula:

$$TOTAL\ MOE = \frac{NOAEL\ (mg/kg/day)}{Dermal\ Dose\ (mg/kg/day) + Inhalation\ Dose\ (mg/kg/day)}$$

Handlers Exposure and Risk

HED's level of concern for the MOE is defined by the uncertainty factors that are applied to the assessment. HED applies a 10X factor to account for inter-species extrapolation and a 10X factor to account for intra-species sensitivity. The total uncertainty factor that has been applied to the non-cancer risk assessment for thiamethoxam is 100 for occupational exposure. Occupational exposure and risk resulting in MOEs greater than or equal to 100 will not be of concern to HED.

Foliage treatment within greenhouses may be performed using various overhead and handheld spray and fogger systems (i.e., thermal foggers). HED does not have specific unit exposures values for these scenarios; however, HED has used surrogate exposure values for groundboom and handheld spray equipment to simulate and estimate exposure resulting from these types of greenhouse equipment.

Summaries of the risks for handlers are included in **Table 5.1**. The maximum application rate for each exposure scenario is presented as the worst case scenario. All handler scenarios resulted in total MOEs greater than the level of concern (MOEs $\geq$ 100). Therefore, all handler exposure scenarios (including those listed in Table 3 with lower application rates) were not of concern to HED. With the exception of the flagger scenario, the calculated MOEs include use of PPE (gloves; also respirator and protective eye ware for the fogger scenario) or engineering controls for aerial applicators.

Table 5.1. Agricultural Handler Exposure and Risk for Thiamethoxam											
Product & Formulation	**Method of Application**	**Mitigation**	**Use Site**	**Dermal Unit Exposure (mg/lb ai)**	**Inhalation Unit Exposure (mg/lb ai)**	**Application Rate (lb ai/A) or (lb ai/gal)**	**Amount Treated (Acres/day or gals/day)**	**Dermal Dose (mg/kg/day)**	**Inhalation Dose (mg/kg/day)**	**Total Dose (mg/kg/day)**	**Total MOE**
Mixer/loader											
Flagship 25% ai WDG	chemigation	Single layer w/ gloves .	Ornamental plants, fruiting vegetables and cucurbit plant seedlings, non bearing fruit and nut trees, forest seedling and Christmas trees	0.066	0.00077	0.266 lb ai/A or 0.00133 lb ai/gal	350 A	0.0051	0.0012	0.0063	190
	ground		Ornamental plants, fruiting vegetables and cucurbit plant seedlings, forest seedling, Christmas trees and turf and grass surrounding potted plants and nursery				80 A	0.0011	0.0003	0.0014	830
	airblast		Non-bearing fruit and nut trees, Christmas trees				40 A	0.0006	0.0001	0.0007	1700
	aerial		Ornamental plants, forest seedling, Christmas trees				350 A	0.0051	0.0012	0.0063	190
Applicator											
Flagship 25% ai WDG	groundboom	Single layer & gloves	Ornamental plants, fruiting vegetables and cucurbits plant seedlings, non bearing fruit and nut trees, forest seedling, Christmas trees	0.014	0.00074	0.266 lb ai/A	80 A	0.0002	0.0003	0.0005	2300
	airblast	Baseline	Non-bearing fruit and nut trees, Christmas trees	0.36	0.0045		40 A	0.0032	0.0008	0.0039	300
	aerial	Eng.Cont.	Ornamental	0.005	0.000068		360 A	0.0003	0.0001	0.0005	2400

Table 5.1. Agricultural Handler Exposure and Risk for Thiamethoxam											
Product & Formulation	**Method of Application**	**Mitigation**	**Use Site**	**Dermal Unit Exposure (mg/lb ai)**	**Inhalation Unit Exposure (mg/lb ai)**	**Application Rate (lb ai/A) or (lb ai/gal)**	**Amount Treated (Acres/day or gals/day)**	**Dermal Dose (mg/kg/day)**	**Inhalation Dose (mg/kg/day)**	**Total Dose (mg/kg/day)**	**Total MOE**
			plants, forest seedling, Christmas trees								
Flagger											
Flagship 25% ai WDG	Flagging for Aerial Sprays Applications (PHED)	Single layer no gloves	Ornamentals, and forest seedling, Christmas trees	0.011	0.00035	0.266	350 A	0.0008	0.0005	0.0014	860
Mixer/loader/Applicator											
Flagship 25 WDG	Backpack (PHED)	Single layer w/gloves	Ornamental plants, fruiting vegetables and cucurbit plant seedlings, non bearing fruit and nut trees, forest seedlings, Christmas trees	2.5	0.03	0.00133 lb ai/gal	40 gals	0.0001	2.66e-5	0.0001	8800
	Low pressure handwand (PHED) liquid			0.43	0.03			0.000019	2.66e-5	0.000045	26,000
	Hose-end Sprayer (PHED)		Turf and grass surrounding potted plants and nursery	34	0.0095			0.0015	8.42E-6	0.0015	790
	High Pressure Handwand (PHED)			2.5	0.12		1000 gals	0.0027	0.0026	0.0054	220
		PF10 resp and protective eye ware	Greenhouses (simulating fogger)	2.5	0.012			0.0027	0.000266	0.0029	410

a. Unit Exposures based on PHED Version 1.1
b. Application Rates based on proposed registered labels for Thiamethoxam products
c. Science Advisory Council Policy # 9.1
d. Dermal Dose (mg/kg/day) = [Rate (lb ai/A) x UE (mg /lb ai) x Acres Treated (A/day)/ BW (60 kg)] x 5% DA
e. Inhalation Dose (mg/kg/day) = [Rate (lb ai/A) x UE (mg /lb ai) x Acres Treated (A/day)] / BW (60 kg)
f. Total Dose (mg/kg/day) = Dermal Dose (mg/kg/day) + Inhalation Dose (mg/kg/day)
g. Total MOE = [NOAEL (1.2 mg/kg/day)]/ Total Dose (mg/kg/day)

5.2 Postapplication Exposure

Dermal exposures during postapplication activities were estimated using dermal transfer coefficients from the Science Advisory Council For Exposure Policy Number 3.1: Agricultural Transfer Coefficients, August 2000, chemical specific turf transferable residue (TTR) data previously reviewed and summarized (M. Collantes; March 2007; D332064), a chemical specific dislodgeable foliar residue (DFR) study for ornamentals and the following assumptions:

Assumptions:

- Application Rate = range from 0.023 lb ai/A to 0.266 lb ai/A
- Exposure Duration = 8 hours per day
- Body Weight = 60 kg
- Dermal Absorption = 5%
- Fraction of a.i. retained on foliage is assumed to be 20% (0.2) on day zero (= % dislodgeable foliar residue, DFR, after initial treatment) for agricultural crops (fruit, nut and evergreen trees). This fraction is assumed to further dissipate at the rate of 10% (0.1) per day on following days. These are default values established by HED's Science Advisory Council (SAC) for Exposure.

Data:

1. ***Determination of Transferable Turf Residues on Turf Treated with Granular and Water Dispersible Granular Formulation of Thiamethoxam. L. Rosenheck, MRID 46402915***

This study was designed to characterize dissipation of thiamethoxam transferable turf residues when applied to turf at three test sites in California, Pennsylvania and North Carolina. Meridian™ 25WG Insecticide, formulated as a water-dispersible granule containing 25% thiamethoxam as the active ingredient and Meridian™ 0.33G Insecticide, formulated as a dry granule containing 0.33% ai thiamethoxam, were applied once to separate plots at each site. The applications were made using turf handgun equipment and a drop spreader, typical of residential lawn applications. The effect of watering-in versus not watering-in was also examined at each site. Watering-in was conducted by applying 0.25 inches of water following application using overhead sprinkler irrigation. Each Meridian™ 25WG and 0.33G application was made at the maximum target application rate of 0.265 lbs ai per acre. Transferable turf residues (TTR) were collected using the modified California Roller Technique. The application method, rate, and frequency (number and timing) were relevant to the use pattern proposed by the product label. All untreated control samples were collected at each site prior to application of the test product. Each field site consisted of four treated plots: (1) Meridian™ 25WG - non-irrigated; (2) Meridian™ 25WG - irrigated; (3) Meridian™ 0.33G - non-irrigated and (4) Meridian™ 0.33G - irrigated. Each treated plot was divided into subplots from which four replicate samples were collected randomly at each sampling interval.

Only one irrigated Meridian™ 25WG test plot (North Carolina) had measurable transferable residues; these residues were detected at 4 hours and 2 days after treatment (DAT2) and were just slightly above the MQL (0.000359 $\mu g/cm^2$). At the California test site, the maximum

average TTR values for the non-irrigated Meridian™ 25WG application occurred immediately after the application of the test substance (0.0122 μg/cm^2). At the Pennsylvania test site, the maximum average TTR values for the non-irrigated Meridian™ 25WG application occurred immediately after the application of the test substance (0.0096 μg/cm^2). **Table 5.2a** provides a comparison of the Registrant's and HED's half-life values, regression coefficients, as well as a summary of the zero hour average residues' percent of application at each field site.

TABLE 5.2a: Meridian™ 25WG Non-irrigated Trial Summary

Field Site	Registrant's Regression Coefficient (R^2)	Registrant's Half-life (hours)	HED's Regression Coefficient (R^2)	HED's Half-life (days)	Zero Hour Avg Residue (μg/cm^2)	Percent of Average Application Rate
California	0.9792	1.17	0.9798	1.19	0.0122	0.40
Pennsylvania	0.9671	0.361	0.9723	0.356	0.0096	0.31
N.Carolina	0.9486	1.34	0.6767	1.37	0.00174	0.24

2. *Dislodgeable Foliar Residues on Greenhouse Ornamentals Following Foliar Spray with Thiamethoxam (CGA-293343): Pilot Study (MRID# 46033991)*

A small scale greenhouse trial was conducted as a pilot study to determine the level of residues of thiamethoxam dislodged from hydrangea plant foliage under actual greenhouse conditions immediately after one application of Flagship 25™ WG at the proposed maximum label rate of 8.5 oz formulated product per acre with a spray volume of approximately 200 gallons of water per acre. The field trial greenhouses were located at a research facility near Creedmoor, North Carolina. The test product used in the study was Flagship™ 25WG, a water-dispersible granule containing 25% thiamethoxam as the active ingredient (ai). The test product was applied to the foliage in a single directed spray application using a single nozzle low pressure hand gun sprayer. Triplicate dislodgeable foliar residue (DFR) samples were collected from the treated ornamental plants following the application. Control samples were collected from ornamental plants in a greenhouse located nearby in which no Flagship™ 25WG applications were made. Samples were collected from treated replicate plots A, B, and C, prior to and following the application (2-hours) and at 4, 8, 12, and 24 hours after the application. Control leaf punch samples were collected before the application, following the application (2 hours) and 24 hours after the application.

The field study samples required correction for field fortification recoveries. HED corrected the field sample residues using the corresponding low or high level field fortification recoveries of 84.9% and 77.8%, respectively and a midpoint of 52.5 μg/sample. The thiamethoxam DFR values did not vary much in the first 12 hour sampling period and the value at 24 hours, the last sampling period were slightly lower. The highest average residue was observed 12-hours after the application (0.238 μg/cm^2). The average residue at 24 hours after application was 0.155 μg/cm^2.

When **Flagship® 25 WG** is directly applied to the soil it is incorporated well before the crops are mature. Therefore, there is a low potential for post-application exposure and an assessment for these uses is not included in the postapplication assessment.

Table 5.2b: Anticipated Postapplication Activities and Dermal Transfer Coefficients

Crop Group or Site	Transfer Coefficients (cm^2/hr)	Activities	Reference
Non-bearing Fruit and Nut Trees	2500	pruning, scouting	Central value from MRID 430627 – hand pruning citrus
Evergreen (Christmas Trees)	3000	Pruning cones, hand pruning	Central value from MRID 430627 – hand pruning citrus
Ornamentals	110	Outdoor ornamental pruning and tying	MRID 45469501; ARTF Study No. ARF043
	175	Greenhouse hand pinching ornamentals	MRID 45344501; ARTF Study No. ARF039
	400	Ornamentals in 5, 7, and 15 gallon pots; workers moving plants into trucks	MRID 45469502; ARTF Study No. ARF044
	5100 (short-term) 2700 (intermediate -term)	Cut flowers	
Turf	3400	Scouting, weeding, fertilizing, aerating, mowing, irrigation	Chlorothalonil mowing study

The information in the table is based on proprietary and non-proprietary data.

Equations/Calculations:

The following equations were used to calculate risks for workers performing postapplication activities:

DFRt (ug/cm2) = Application Rate (lb ai/acre) x F x (1-D)^t x 4.54E8 µg/lb x 24.7E-9 acre/cm^2

Where:

DFR_t = dislodgeable foliage residue on day "t" (ug/cm^2)
Rate = application rate (lb ai/acre)
F = fraction of ai retained on foliage (unitless)
D = fraction of residue that dissipates daily (unitless)

and

$$\text{Daily dermal dose}_t = \frac{DFR_t\ (\mu g/cm^2) \text{ or } TTR\ (\mu g/cm^2) \times 1E\text{-}3\ mg/\mu g \times Tc\ (cm^2/hr) \times DA \times ET\ (hrs)}{BW\ (kg)}$$

Where,

t	=	number of days after application day (days)
DFR_t	=	dislodgeable foliage residue on day "t" (ug/cm^2)
TTR	=	turf transferable residue on day "t" (0.0122 $\mu g/cm^2$)
Tc	=	transfer coefficient (cm^2/hr)
DA	=	dermal absorption factor (unitless)
ET	=	exposure time (hr/day)
BW	=	body weight (kg)

Exposure and Risk

The dermal postapplication exposure associated with agricultural crops, ornamentals including cut flowers and turf is summarized in **Table 5.2.1**. All postapplication scenarios resulted in MOEs greater than or equal to 100 and therefore are not of concern to HED.

Table 5.2.1 : Dermal Postapplication Exposure and Risk for Thiamethoxam

Crops	DAT	DFR [2a & 2b] / TTR [2c] (ug/cm^2)	Daily Dose (mg/kg/day) [3]		MOE	
			Low	High	Low	High
Fruit trees Nut Trees	0	0.596	NA	0.0099	NA	120
Evergreen				0.0119		100
Ornamentals (cut flowers)		0.238	0.0042	0.0080	280	150
Turf and grass		0.0122 [b]	NA	0.00027	NA	4,300

1. DAT = Days after treatment

2a. trees (fruit, nut and evergreen) DFR = Dislodgeable Foliar Residue = application rate (lb ai/A) x (1- daily dissipation rate)^t x 4.54E8 ug/lb x 24.7E-9 A/cm2 x 20% DFR after initial treatment.

2b. ornamental DFR based on chemical specific data from the greenhouse ornamental study MRID 46033991

2c. TTR = Turf Transferable Residue = 0.0122 ug/cm^2 – chemical specific data submitted in support of this action

3. Daily Dose = [DFR (ug/cm^2) or TTR (ug/cm^2) x Tc (cm^2/hr) x 0.001 mg/ug x 5% dermal absorption x 8 hrs/day] ÷ body weight (60 kg)

4. MOE = NOAEL/Daily Dose (Adult Dermal NOAEL = 1.2 mg/kg/day).

There is potential for inhalation postapplication exposure resulting from the use of thiamethoxam in greenhouses. However thiamethoxam has a low vapor pressure (4.95×10^{-11} mm Hg). The proposed use on ornamentals and cut flowers also includes application in greenhouses. The Worker Protection Standards (WPS) for Agricultural Pesticides contains requirements for protecting workers from inhalation exposures during and after greenhouse applications through the use of ventilation requirements. Therefore, inhalation exposure is expected to be negligible and a quantitative postapplication inhalation exposure assessment was not performed.

Restricted Entry Interval

The restricted entry interval (REI) is based on the acute toxicity of thiamethoxam technical material which is classified as Category III for acute oral and Category IV for acute dermal and

eye irritation. Thiamethoxam is not a dermal sensitizer. Acute toxicity categories III and IV chemicals require a 12- hour REI. Therefore, the 12-hour REI which appears on the proposed label is adequate.

13544

R176941

Chemical Name: Thiamethoxam

PC Code: 060109
HED File Code: 12000 Exposure Reviews
Memo Date: 9/9/2009
File ID: 00000000
Accession #: 000-00-0130

HED Records Reference Center
9/29/2009